Mahmood, A., Suarez, J. R., Thomas, S. P., & Aggarwal, V. K. (2013). One-pot synthesis of 2,3,4,5,6-pentasubstituted tetrahydropyrans using lithiation-borylation, allylation and Prins cyclisation reactions. *Tetrahedron Letters*, *54*(1), 49-51. https://doi.org/10.1016/j.tetlet.2012.10.091

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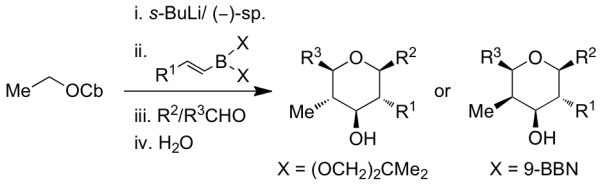
Adeem Mahmood, Jose Ramón Suárez, Stephen P. Thomas and Varinder K. Aggarwal*
School of Chemistry, University of Bristol, Cantock's Close, Bristol, BS8 1TS



Tetrahedron Letters
journal homepage: www.elsevier.com

One-pot synthesis of 2,3,4,5,6-pentasubstituted tetrahydropyrans using lithiation-borylation, allylation and Prins cyclisation reactions

Adeem Mahmood[†], Jose Ramón Suárez, Stephen P. Thomas and Varinder K. Aggarwal*

School of Chemistry, University of Bristol, Cantock's Close, Bristol, BS8 1TS

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Lithiation-borylation
Allylation
Prins Cyclisation
Tandem
Boronic ester

ABSTRACT

2,3,4,5,6-Pentasubstituted tetrahydropyrans have been prepared in good yield (42-57%) with excellent *dr* (>95:5) and *er* (>95:5) using a one-pot lithiation-borylation, allylation and Prins cyclisation reaction.

* Corresponding author. Tel.: +44(0)117 954 6315; fax: +44(0)117 925 1295; e-mail: V.Aggarwal@bristol.ac.uk

[†] Current address; Department of Chemistry, COMSATS Institute of Information Technology, Abbottabad-22060, Pakistan

Substituted tetrahydropyrans (THPs) are ubiquitous in nature.[1] They show great diversity in structure and complexity, from the relatively simple tri-substituted THP (–)-diospongin A[2] to the highly complex polyketide marine metabolites clavosolide A[3] and (–)-kendomycin[4] with penta-substituted THP cores (Figure 1). One of the most efficient strategies for their construction involves the Prins cyclisation,[5] as demonstrated by numerous research groups.[5a, 6] Indeed, the acid-catalysed Prins cyclisation of an in situ generated oxocarbenium ion has been extensively used for the stereoselective synthesis of diversely functionalised THPs.[7] Although allyltin[8] and allylsilyl[9] reagents have been used in this context, to the best of our knowledge, there is only a single report of allylboron reagents being used for the stereoselective synthesis of racemic THPs using a tandem allylation and Prins cyclisation.[10]

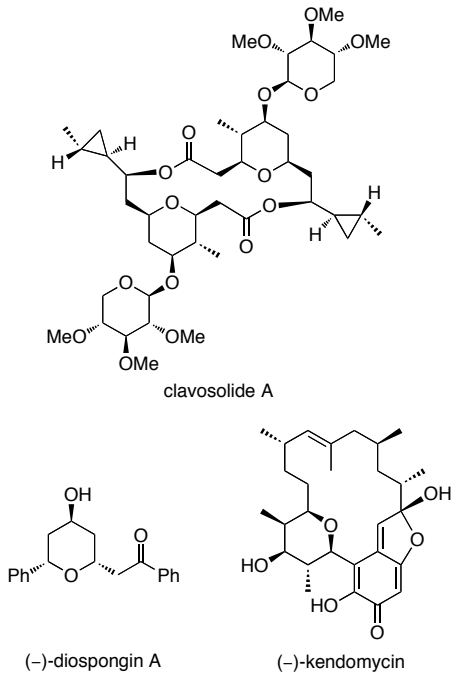


Figure 1. THP containing natural products.

We recently reported the enantioselective synthesis of α-substituted allylic boron reagents which could be reacted with aldehydes to give homoallylic alcohols with control of all elements of stereochemistry (*syn*/*anti*; *E*/*Z*).[11] We recognised that if these products could be used in a subsequent Lewis acid-catalysed Prins cyclisation we would have the ability to form highly substituted THPs with excellent diastereoselectivity and enantioselectivity.

We postulated that if the allylation products, **6** or **7** formed *via* an initial allylation with the first equivalent of aldehyde, could be trapped by a second aldehyde in the presence of a Lewis acid, a Prins cyclisation should ensue (**8→10** or **9→11**) to give highly substituted THPs (Figure 2). The enantioselectivity would be set in the lithiation-borylation reaction (>98:2 *er*) and the diastereoselectivity would be set in the allylation reaction (>95:5 *dr*), and subsequent Prins cyclisation.

Significantly, the substituents on boron could be exploited to favour one of two transition-state structures (TS) **4** and **5** in the initial allylation reaction with the first aldehyde. Large substituents on boron (eg 9-BBN) would cause a steric clash between R^1 and the boron substituents,[13] thereby favouring the allylation product arising from TS **4**. This would give the (*Z*)-alkene which, after Prins cyclisation, would give the 3,5-*anti*-THP **12** after work-up. Use of small boron substituents (eg $(OCH_2)_2CMe_2$) reduces the steric clash between R^1 and the boron substituents[14] and now TS **5** bearing the equatorial substituent would be favoured due to competing $A^{1,3}$ strain in TS **4**. This would lead to the (*E*)-alkene which, following Prins cyclisation and trapping by water, would give the all equatorial substituted THP **13**, with the 3,5-*syn* arrangement.

Furthermore, the sequential nature of our proposed THP synthesis presents the possibility for a one-pot synthesis of fully differential THPs from the addition of two different aldehydes. The 3- and 5-substituents arise from the carbamate **1** and boron reagent **2** and the 2- and 6-substituents from the aldehydes used in the allylation and Prins reactions, respectively.

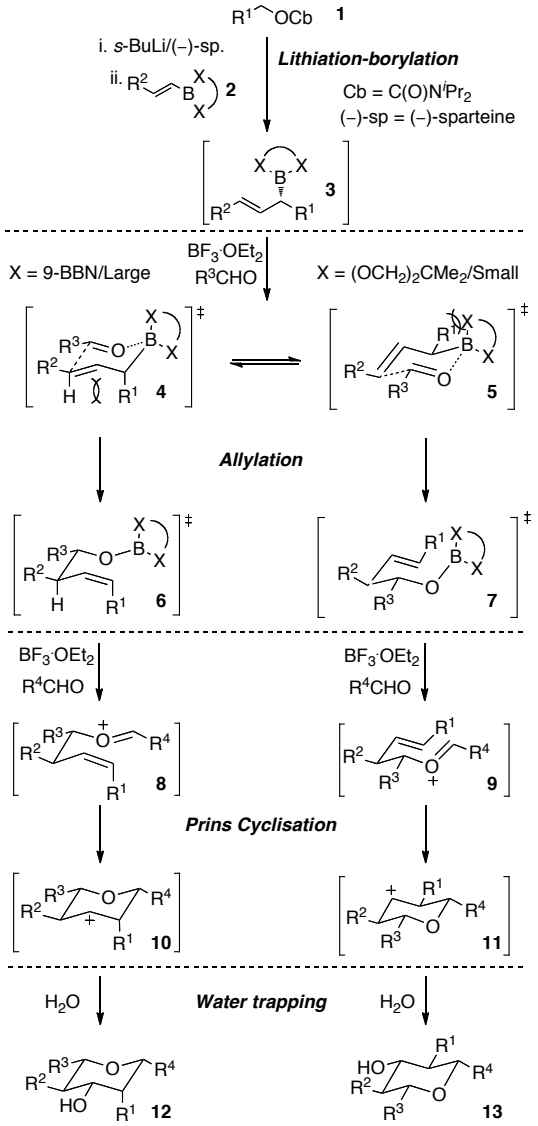


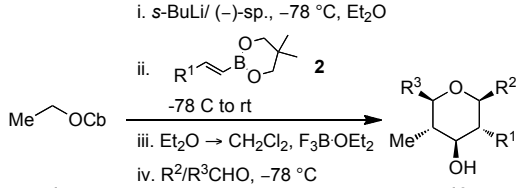
Figure 2. Proposed synthesis of highly substituted THPs using lithiation-borylation, allylation and Prins cyclisation.

Our studies began by targeting the all equatorial substituted THPs **13** (Table 1, entries 1-6). To favour TS **5**, neopentylglycol boronic esters were used along with a similar allylation protocol to that which we had previously used with great success.[11] Thus, deprotonation of ethyl carbamate **1** with s-BuLi in the presence of (–)-sparteine followed by addition of vinyl boronic ester **2** gave an intermediate ate complex. To promote 1,2-metallate rearrangement, and thus formation of the allylboronic ester **3** (X = $(OCH_2)_2CMe_2$), a solvent exchange was carried out from Et_2O to CH_2Cl_2 and $BF_3.OEt_2$ was added. Subsequent addition of an

excess of either cyclohexylcarboxaldehyde or benzaldehyde (these were used as representative aldehydes) and further addition of $BF_3{\cdot}OEt_2$ followed by aqueous workup gave the THPs in moderate yield but very high enantioselectivity and very high diastereoselectivity. In the one-pot process 3 C-C bonds, and 2 C-O bonds have been formed and 5 stereogenic centres have been controlled. The use of a variety of boronic esters was examined including Me- (entries 1,2), Bu- (entries 3,4) and H- (entries 5,6). In all cases excellent stereocontrol was observed even with the parent unsubstituted vinylboronic ester (R^1 = H, entries 5,6). Interestingly, no addition of fluoride was observed in the 4-position as might be expected when using BF_3 in the absence of a fluoride trap.[15,16]

The use of two different aldehydes in the sequential allylation, Prins cyclisation was also explored as this would lead to a fully differentially substituted THP, a significantly greater challenge.[5a] However, by simply adding the two different aldehydes in sequence we were able to obtain the 2,6-differentially substituted THPs in good yield and excellent *dr* and *er* (table 1, entry 7-10). In one case (table 1, entry 9), when cyclohexylcarboxaldehyde was used as the first aldehyde (followed by benzaldehyde), we observed a significant amount the bis-cyclohexyl substituted THP. In contrast, use of benzaldehyde as the first aldehyde followed by cyclohexylcarboxaldehyde gave the required THP with complete control over the substitution at each THP-carbon (entry 8). Presumably, the lower selectivity of former reaction can be explained by the decreased reactivity of benzaldehyde compared to cyclohexylcarboxaldehyde.

Table 1. Synthesis of 2,3,4,5,6-pentasubstituted THPs using neopentlyglycol boronic esters.[a,b]



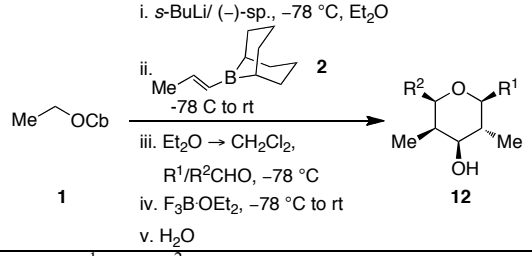
Entry	R^1	R^2	R^3	Yield(%)	*dr*	*er*
1[a]	Me	Ph	Ph	54	>95:5	96:4
2[a]	Me	Cy	Cy	51	>95:5	-
3[a]	Bu	Ph	Ph	52	>95:5	98:2
4[a]	Bu	Cy	Cy	57	99:1	-
5[a]	H	Ph	Ph	45	>95:5	98:2
6[a]	H	Cy	Cy	49	>95:5	-
7[b]	Bu	Cy	Ph	50	>95:5	96:4
8[b]	Bu	Ph	Cy	48	>95:5	95:5
9[b]	Me	Cy	Ph	54[c]	>95:5	97:3
10[b]	H	Cy	Ph	44	>95:5	97:3

[a] $R^2 = R^3$ (i) *s*-BuLi (1.4 eq.), (–)-sp. (1.4 eq.), Et_2O (0.17 M), -78 °C, 5h. (ii) **2** (1.7 eq.), -78 °C to rt, 2.5h. (iii) Et_2O to CH_2Cl_2, $F_3B{\cdot}OEt_2$ (2 eq.), rt, 0.5h. (iv) R^2CHO (4 eq.), -78 °C, 1h. (v) $F_3B{\cdot}OEt_2$ (2 eq.), -78 °C to rt, 18h. (vi) H_2O, rt, 3h. [b] $R^2 \neq R^3$ (i) *s*-BuLi (1.4 eq.), (–)-sp. (1.4 eq.), Et_2O (0.17 M), -78 °C, 5h. (ii) **2** (1.7 eq.), -78 °C to rt, 2.5h. (iii) Et_2O to CH_2Cl_2, $F_3B{\cdot}OEt_2$ (2 eq.), rt, 0.5h. (iv) R^2CHO (1.5 eq.), -78 °C, 1h. (v) R^3CHO (3 eq.), -78 °C, 1h. (vi) $F_3B{\cdot}OEt_2$ (2 eq.), -78 °C to rt, 18h. (vii) H_2O, rt, 3h. [c] Isolated as a 2:1 mixture of 2-Ph-6-c.Hex- and 2,6-di-c.Hex-THP.

We next turned our attention to the synthesis of the diastereomeric 3,5-*anti*-THPs **12** (Table 2). To favour TS **4**, a bulky substituent at boron was required and the *B*-9-BBN group was selected. Furthermore, the increased reactivity of boranes in the lithiation-borylation reaction[17] negated the need for Lewis acids to trigger 1,2-metallate rearrangement, although a solvent exchange to CH_2Cl_2 was still needed to effect efficient Prins cyclisation.

Thus, deprotonation of ethyl carbamate **1** with s-BuLi in the presence of sparteine followed by addition of *B*-vinyl-9-BBN gave an intermediate ate complex which underwent rapid 1,2-metallate rearrangement at low temperature. Solvent exchange from Et_2O to CH_2Cl_2 followed by addition of an excess of either cyclohexylcarboxaldehyde or benzaldehyde, followed by further addition of $BF_3{\cdot}OEt_2$ gave the THPs in moderate yield but very high enantioselectivity and diastereoselectivity. Once again, excellent levels of stereocontrol were observed using both aryl- and alkyl aldehydes giving excellent *dr* and *er* (entries 1-2) and the sequential addition of two different aldehydes could be used to differentiate the 2- and 6-positions with excellent *dr* and *er* (entry 3). The use of the *B*-9-BBN reagents giving the highest levels of diastereoselectivity reported herein. Presumably the large 9-BBN group significantly shifts the TS equilibrium towards **4** in the allylation reaction and increased reactivity of the intermediate borinic esters increases the rate of aldehyde exchange and Prins cyclisation.

Table 2. Synthesis of 2,3,4,5,6-pentasubstituted THPs using *B*-9-BBN boranes.[a,b]



Entry	R^1	R^2	Yield (%)	*dr*	*er*
1[a]	Ph	Ph	48	>95:5	95:5
2[a]	Cy	Cy	45	>95:5	-
3[b]	Cy	Ph	42[c]	>95:5	97:3

[a] $R^1 = R^2$ (i) *s*-BuLi (1.4 eq.), (–)-sp. (1.4 eq.), Et_2O (0.17 M), -78 °C, 5h. (ii) **2** (1.7 eq.), -78 °C to rt, 2.5h. (iii) Et_2O to CH_2Cl_2, R^1CHO (4 eq.), -78 °C, 1h. (iv) $F_3B{\cdot}OEt_2$ (4 eq.), -78 °C to rt, 18h. (v) H_2O, rt, 3h. [b] $R^1 \neq R^2$ (i) *s*-BuLi (1.4 eq.), (–)-sp. (1.4 eq.), Et_2O (0.17 M), -78 °C, 5h. (ii) **2** (1.7 eq.), -78 °C to rt, 2.5h. (iii) Et_2O to CH_2Cl_2, R^1CHO (1.5 eq.), -78 °C, 1h. (iv) R^2CHO (3 eq.), -78 °C, 1h. (v) $F_3B{\cdot}OEt_2$ (4 eq.), -78 °C to rt, 18h. (vi) H_2O, rt, 3h. [c] Isolated as a 1:1 mixture of 2-Ph-6-c.Hex- and 2,6-di-c.Hex-THP.

In summary we have developed a one-pot synthesis of functionalised tetrahydropyrans using a sequential lithiation-borylation, allylation and Prins cyclisation reaction. The protocol has been successfully applied to the highly diastereo- and enantioselective syntheses of 2,3,4,5,6- and 2,3,4,5-substituted THPs.

1. Acknowledgments

We thank the EPSRC National Mass Spectrometry Service centre of providing high-resolution mass spectra and Inochem-Frontier Scientific for the generous donation of organoboron reagents. VKA thanks the EPSRC for a Senior Research Fellowship and the Royal Society for a Wolfson Research Merit Award. AM thanks the Higher Education Commission of Pakistan and the University of Bristol for a PhD studentship. JRS thanks the Spanish Ministerio de Educación y Ciencia for a postdoctoral fellowship.

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